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09/787,394	05/16/2001	Naoto Miwa	SCH 1799	2377

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EXAMINER	
CAPPS, KEVIN J	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/787,394	MIWA ET AL.	
	Examiner	Art Unit	
	Kevin Capps	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,36-42 and 46-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31, 32, 36-42, and 46-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. This Office Action is in response to the Remarks and Amendments filed on January 25, 2007. Claims 31, 32, 36-42, and 46-53 are pending and examined on the merits herein.

2. Claims 31, 32, 36-42, and 46-53 stand rejected under 35 USC § 103 over Licha et al. (US 6,083,485 and/or US 6,258,340. Both documents contain the same disclosure.). The rejection is maintained and restated to address Applicant's amendments. Applicant's arguments are addressed below.

3. Claims 31, 32, 36-42, and 46-53 stand rejected under 35 USC § 103 over Licha et al. (US 6,083,485 and/or US 6,258,340. Both documents contain the same disclosure.) in view of Ohno et al. (US 4,839,265). The rejection is maintained and restated to address Applicant's amendments. Applicant's arguments are addressed below.

4. Claims 31, 32, 36-42, and 46-53 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35-44 of copending Application No. 10/324,010. The rejection is maintained and restated to address Applicant's amendments. Applicant has provided no rebuttal arguments against the rejection.

5. Claims 31, 32, 36-42, and 46-53 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-

22 and 24-26 of copending Application No. 10/149,917. Note that the in the previous Office Action, it was stated that the rejection was over 10/419,917. This was a typographical error. The rejection was actually over 10/149,917, which is an application by the instant inventor. The rejection is maintained and restated to address Applicant's amendments. Applicant has provided no rebuttal arguments against the rejection.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 31, 32, 36-42, and 46-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Licha et al. (US 6,083,485 and/or US 6,258,340. Both documents contain the same disclosure. Citations refer to '485 unless specifically noted otherwise.)

9. Licha et al. teach a method of in vivo imaging comprising administering a genus of compounds that encompasses compounds of the instant formula III-1 (claim 1 of

'340; col. 4, line 64-col. 6, line 14). Licha et al. teach that the compounds can have sulfonic acid groups (see, for example, col. 5, line 21). Licha et al. teach that the compounds can be administered in combination with a pharmaceutically acceptable carrier (col. 14, lines 41-52). Licha et al. teach that the in vivo imaging method is for angiography and tumor imaging (col. 1, line 66-col. 2, line 6; col. 9, lines 30-34; col. 13, lines 26-31).

10. Licha et al. do not exemplify compounds of the instant formula III-1 as preferred for use in the in vivo imaging method. Licha et al. do not teach that when a compound containing a sulfonic acid group is selected from within their genus of compounds for use in the in vivo imaging method, the sodium salt of the sulfonic acid substituent is preferred.

11. It would have been obvious to the person of ordinary skill in the art at the time of invention to administer the compounds of the instant formula III-1 in a method of in vivo imaging for angiography and/or tumor imaging. It would have further been obvious to administer the compounds of the instant formula III-1 as sodium salts.

12. The person of ordinary skill in the art would have been motivated to administer the compounds of the instant formula III-1 for in vivo imaging because Licha et al. teach a genus of compound encompassing the instant compounds that are effective for in vivo imaging of blood flow and tumors. Because Licha et al. teach that the entire genus of compounds is effective for in vivo imaging, the person of ordinary skill in the art would have expected, absent evidence to the contrary, that any of the compounds selected from within the genus disclosed by Licha et al., including the compounds of the instant

formula III-1, would be effective for in vivo imaging. Further, it has been established that it is obvious to form a salt from a known acid. *In re Williams*, 89 USPQ 396 (CCPA 1951). Thus, it would have been obvious to the person of ordinary skill in the art to administer the sulfonic acid-containing compounds of Licha et al. as sodium salts in imaging methods.

13. Claims 31, 32, 36-42, and 46-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Licha et al. as applied to claims 31, 32, 36-42, and 46-53 above, and further in view of Ohno et al. (US 4,839,265).

14. As discussed above, Licha et al. teach in vivo imaging methods for angiography and tumor imaging comprising administering a genus of compounds encompassing compounds of the instant formula III-1.

15. Licha et al. do not exemplify compounds of the instant formula III-1 as preferred for use in the in vivo imaging method. Licha et al. do not teach that when a compound containing a sulfonic acid group is selected from within their genus of compounds for use in the in vivo imaging method, the sodium salt of the sulfonic acid substituent is preferred.

16. Ohno et al. teach compounds within the scope of the compounds administered in the imaging method of Licha et al. that are also within the scope of the instant formula III-1. Notably, Ohno et al. exemplify sodium salts of these compounds (see: compounds (I-3), (I-5), (I-7), (I-11), and (I-12); col. 3, lines 19-25). Ohno et al. teach that the compounds are photosensitive and that they are dyes.

17. It would have been obvious to the person of ordinary skill in the art at the time of invention to administer the compounds exemplified by Ohno et al. as the sodium salts, which are within the genus of compounds taught by Licha et al., in a method of imaging for angiography and/or tumor imaging, to arrive at the instantly claimed method.

18. The person of ordinary skill in the art would have been motivated to administer the compounds of Ohno et al. for in vivo imaging because Ohno et al. exemplify compounds of the instant formula III-1 that are within the genus of compounds taught by Licha et al. that are effective for in vivo imaging of blood flow and tumors, and Ohno et al. also teach how to make the compounds, i.e., obtain the compounds. Further, the person of ordinary skill in the art would have been motivated to administer the compounds of Ohno et al. in the method of Licha et al. because Ohno et al. teach that the compounds are photosensitive and they are dyes. Therefore the person of ordinary skill in the art would have expected them to be effective in the method of imaging taught by Licha et al. Because Licha et al. teach that the entire genus of compounds encompassing the compounds of the instant formula III-1 is effective for in vivo imaging, the person of ordinary skill in the art would have expected, absent evidence to the contrary, that any of the compounds selected from within the genus disclosed by Licha et al., including the compounds exemplified by Ohno et al., would be effective for in vivo imaging.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 31, 32, 36-42, and 46-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35-44 of copending Application No. 10/324,010. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to methods of using the same compounds for in vivo imaging.

21. '010 teaches a method of imaging in a living body comprising administering compounds that overlap in scope with the compounds administered in the instantly claimed method.

22. '010 does not teach all of the herein-claimed preferred compounds.

23. It would have been obvious to the person of ordinary skill in the art to select the instant compounds of formula III-1 and to administer them in a method of imaging, particularly for angiography or tumor imaging.

24. The person of ordinary skill in the art would have been motivated to select the compounds of the instant formula III-1 and administer them for imaging because they are within the scope of the compounds taught in '010, and '010 teaches that all of the compounds are effective for imaging. Thus, the person of ordinary skill in the art would have expected success administering any of the compounds taught in '010 for imaging because they are taught to be equivalents for imaging purposes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claims 31, 32, 36-42, and 46-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim16-22 and 24-26 of copending Application No. 10/149,917. Although the conflicting claims are not identical, they are not patentably distinct from each other because '917 anticipates the instantly claimed method.

26. '917 teaches a method of imaging for angiography and/or tumor imaging comprising administering a compound within the scope of the instantly claimed method (see the first compound of claim 1). Thus, '917 anticipates the instantly claimed method.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

27. Applicant's arguments filed January 25, 2007, have been fully considered but they are not persuasive.

28. Regarding the rejection of claims 31, 32, 36-42, and 46-53 under 35 USC § 103 over Licha et al. (US 6,083,485 and/or US 6,258,340), Applicant argues that Licha et al. only disclose a genus encompassing the compounds recited in the instant claims, and that there is no motivation to select the specific compounds instantly recited from within the genus. However, as discussed in the previous Office Action and not addressed by Applicant in the latest Remarks, because Licha et al. disclose that the entire genus of compounds is effective for in vivo imaging, the ordinary skilled artisan would expect, absent evidence to the contrary, that any of the compounds from within the genus could be successfully employed in a method of *in vivo* imaging. It is noted that Applicant has provided no reasons why the ordinary skilled artisan would not expect some of the compounds to be effective. Thus, because Applicant has shown no reason to expect that some of the compounds would not be effective for *in vivo* imaging, the *prima facie* case of obviousness has not been rebutted.

29. Applicant further argues that even if the rejection were proper, then the alleged unexpected results of record would rebut the *prima facie* case of obviousness. Applicant specifically points to the decreased toxicity of the sodium salts of the compounds of formula III-1 relative to the potassium salts as being an unexpected result. The Examiner discussed these results in the previous Office Acton, stating "in order to be significant, the toxicity data should be relevant to the amount of the

compounds to be administered in the method, i.e., the toxicity matters only if the compounds are to be administered in that dose range." (see the discussion in paragraph 19 in the Office Action mailed on August 25, 2006). The Examiner concluded that because the compounds are administered in the instantly claimed method at a concentration far below the toxicity levels of both compounds, "the data is not considered to be significant to the instantly claimed method."

30. In the Remarks filed on January 25, 2007, Applicant again argues that the data is of practical significance. Applicant specifically argues, "The examiner's logic totally ignores the fundamental fact of pharmaceutical design that it is important for any agent to be administered to a living body that the difference between toxic doses and therapeutically effective doses be as large as possible." (p. 8 of Remarks). Applicant points to a pharmaceutical parameter called the "therapeutic index" as evidence that the difference between toxic doses and therapeutically effective doses is desirably as large as possible. Applicant points to a range of literature reporting the significance of the therapeutic index, and Applicant also provides alleged therapeutic indexes of the sodium and potassium salts of the compounds of the instant formula III-1. Applicant concludes that because "it is also relevant and important that the difference between effective dose and LD_{50} be made as large as possible for clinical safety purposes", then "the data of record are 'significant and practical' in the context of the claimed method." (p. 9 of Remarks).

31. However, the data of record does not indicate that the toxicity of the compounds is relevant to the instantly claimed method for the following reasons. First, the

references provided by Applicant directly contradict the assertion that the dose ranges are irrelevant to the toxicity levels of the compounds employed in a given method. For instance, Applicant points to "the excerpt from the Boston University Medical Campus stating in its definition of 'Clinical Therapeutic Index,' 'that the assumption is retained that an improved or 'better' drug has a *higher* Clinical Therapeutic Index.'" (p. 9 of Remarks). However, reading the definition supplied in the document is informative in showing why the dose range is critical in considering the relevance of the Clinical Therapeutic Index. The definition states, "The Food and Drug Administration has considered the following definition of an *improved* Clinical Therapeutic Index to be used in comparing different drug combinations or formulations; the assumption is retained that an improved or 'better' drug has a *higher* Clinical Therapeutic Index' (1) increased safety (or patient acceptance) at an accepted level of efficacy **within the recommended dosage range**, or (2) increased efficacy at equivalent levels of safety (or patient acceptance) **within the recommended dosage range**." (emphases added). Thus, even the excerpt from the Boston University Medical Campus cited by Applicant highlights that the recommended dosage ranges are critical in evaluating the significance of the Clinical Therapeutic Index. Because the concentration at which both the sodium and potassium salts become toxic are far above the amounts needed for in vivo imaging, the higher Clinical Therapeutic Index of the sodium salts relative to the potassium salts is not significant.

32. The section of Goodman & Gilman's further supports this conclusion. It states, "since pharmacodynamic variation in the population may be marked, the concentration

or dose of drug required to produce a therapeutic effect in most of the population will usually overlap the concentration required to produce toxicity in some of the population, even though the drug's therapeutic index may be large." (p. 48). However, Figure 3-3 shows that even with a therapeutic index as low as 4, there is substantially no overlap between the effective and lethal doses. On p. 9 of the instant Remarks, Applicant alleges that the therapeutic index of the potassium salts is 70. Thus, in light of the teaching of Goodman & Gilman's, it can be inferred that at such a large therapeutic index, there is virtually no overlap between the toxic and effective doses. Therefore, the increased therapeutic index of the sodium salts relative to the potassium salts is irrelevant because the potassium salts are not even toxic within the effective range. This is, again, because the potassium and sodium salts are both administered far below toxic concentrations for the purpose of *in vivo* imaging.

33. Even if Applicant's arguments concerning the relevance of the therapeutic index were correct, which the Examiner does not concede for the reasons stated above, the arguments are not relevant because Applicant has not even supplied the therapeutic indexes of the compounds. On p. 9 of the Remarks filed on January 25, 2007, Applicant does report some data for the compounds that is referred to as a "therapeutic index". However, this is not the therapeutic index, as commonly defined in the art. Goodman & Gilman's, the reference cited by Applicant, defines therapeutic index as the "ratio of the LD_{50} to the ED_{50}" (p. 48). Goodman & Gilman's defines ED_{50} as the "dose of a drug required to produce a specified effect in 50% of the population" (p. 48). The 5 mg/kg value used by Applicant to calculate the therapeutic index is not the ED_{50}; it is

simply one dose exemplified in the instant specification. No data has been presented that allows one of ordinary skilled artisan to extrapolate the ED_{50} of the sodium and potassium salts. Therefore, the data provided by Applicant is not, by definition, the therapeutic indexes of the sodium and potassium salts, and it would be impossible to calculate these values based on the data in the instant specification. Even if the ED_{50} values were determined for both series of salts, they would be far below the toxicity levels of both series.

34. Because Applicant has provided no reason to believe that some of the compounds within the genus of Licha et al. would not be effective for *in vivo* imaging, and because Applicant has shown no unexpected results that are practical and significant to the instantly claimed method, the § 103 rejection is properly maintained.

35. Regarding the rejection of claims 31, 32, 36-42, and 46-53 under 35 USC § 103 over Licha et al. (US 6,083,485 and/or US 6,258,340) in view of Ohno et al. (US 4,839,265), Applicant argues that Ohno et al. is not analogous art and thus does not supply motivation to choose the genus of compounds instantly recited in the claims because they disclose use of the compounds as dyes in the field of photography, whereas Licha et al. disclose use of the compounds as dyes for *in vivo* imaging. However, as discussed in the previous Office Action, the fact that Ohno et al. disclose that the compounds are dyes is the nexus. The ordinary skilled artisan would understand that the dyes disclosed by Ohno et al. could be used in the method of Licha et al. because they are encompassed by the genus disclosed by Licha et al. and they possess the primary property that makes them useful for in vivo imaging; namely, they

are photosensitive dyes. Also as discussed in the previous Office Action, Ohno et al. teach how to make the compounds, which provides further motivation to select the compounds from within the genus of Licha et al. Finally, as discussed above, Applicant has provided no reason why the ordinary skilled artisan would not expect all of the compounds from within the genus of Licha et al. to be effective for imaging, including the photosensitive dyes exemplified by Ohno et al.

36. Applicant also again argues the significance of the toxicity data of the sodium and potassium salts. However, the toxicity data is not practical or significant for the reasons discussed above.

37. Applicant has provided no rebuttal arguments against the double-patenting rejections.

Conclusion

38. No claims are allowed.

39. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin Capps whose telephone number is (571) 272-8646. The examiner can normally be reached on Monday-Friday, 7:30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KC

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SUPERVISORY PATENT EXAMINER